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The amino-terminal domain of the CCR2 chemokine receptor acts as coreceptor for HIV-1 infection.

J Clin Invest. 1997 Aug 1;100(3):497-502.

PMID: 9239395; UI: 97386611

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HIV-1 coreceptor activity of CCR5 and its inhibition by chemokines: independence from G protein signaling and importance of coreceptor downmodulation.

Virology. 1997 Aug 4;234(2):340-8.

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The amino-terminal domain of CCR2 is both necessary and sufficient for high affinity binding of monocyte chemoattractant protein 1. Receptor activation by a pseudo-tethered ligand.

J Biol Chem. 1997 Sep 12;272(37):23186-90.

PMID: 9287323; UI: 97435284

4: [Hadida F, Vieillard V, Autran B, Clark-Lewis I, Baggiolini M, Debre P.](#) Related Articles

HIV-specific T cell cytotoxicity mediated by RANTES via the chemokine receptor CCR3.

J Exp Med. 1998 Aug 3;188(3):609-14.

PMID: 9687538; UI: 98353546

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Characterization of the CCR2 chemokine receptor: functional CCR2 receptor expression in B cells.

J Immunol. 1997 Dec 1;159(11):5576-84.

PMID: 9548499; UI: 98208279

6: [Gong W, Howard OM, Turpin JA, Grimm MC, Ueda H, Gray PW, Raport CJ, Oppenheim JJ, Wang JM.](#) Related Articles

Monocyte chemotactic protein-2 activates CCR5 and blocks CD4/CCR5-mediated HIV-1 entry/replication.

d 14 1-11

L4 ANSWER 1 OF 11 MEDLINE  
AN 2000413201 MEDLINE  
DN 20361893  
TI Expression of the beta-chemokine receptors CCR2, CCR3 and CCR5 in multiple sclerosis central nervous system tissue.  
AU Simpson J; Rezaie P; Newcombe J; Cuzner M L; Male D; Woodroffe M N  
CS Biomedical Research Centre and Division of Biomedical Sciences, Sheffield Hallam University, City Campus, Pond Street, South Yorkshire, S1 1WB, Sheffield, UK.  
SO JOURNAL OF NEUROIMMUNOLOGY, (2000 Aug 1) 108 (1-2) 192-200.  
Journal code: HSO. ISSN: 0165-5728.  
CY Netherlands  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200011  
EW 20001101

L4 ANSWER 2 OF 11 MEDLINE  
AN 2000384102 MEDLINE  
DN 20351977  
TI Human endothelial cells express CCR2 and respond to MCP-1: direct role of MCP-1 in angiogenesis and tumor progression.  
AU Salcedo R; Ponce M L; Young H A; Wasserman K; Ward J M; Kleinman H K; Oppenheim J J; Murphy W J  
CS Laboratory of Molecular Immunoregulation, Laboratory of Experimental Immunology, Division of Basic Sciences; Intramural Research Support Program, SAIC, Frederick, MD, USA.  
SO BLOOD, (2000 Jul 1) 96 (1) 34-40.  
Journal code: A8G. ISSN: 0006-4971.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
EM 200010  
EW 20001002

L4 ANSWER 3 OF 11 MEDLINE  
AN 2000216633 MEDLINE  
DN 20216633  
TI Exaggerated hepatic injury due to acetaminophen challenge in mice lacking C-C chemokine receptor 2.  
AU Hogaboam C M; Bone-Larson C L; Steinhauser M L; Matsukawa A; Gosling J; Boring L; Charo I F; Simpson K J; Lukacs N W; Kunkel S L  
CS Department of Pathology, University of Michigan Medical School, Ann Arbor,  
Michigan 48109-0602, USA.. hogaboam@path.med.umich.edu  
NC 1P50HL56402 (NHLBI)  
1P50HL60289 (NHLBI)  
CA66180 (NCI)  
+  
SO AMERICAN JOURNAL OF PATHOLOGY, (2000 Apr) 156 (4) 1245-52.  
Journal code: 3RS. ISSN: 0002-9440.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English

FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
EM 200009  
EW 20000901

L4 ANSWER 4 OF 11 MEDLINE  
AN 2000203438 MEDLINE  
DN 20203438  
TI Human intestinal lamina propria and intraepithelial lymphocytes express receptors specific for chemokines induced by inflammation.  
AU Agace W W; Roberts A I; Wu L; Greineder C; Ebert E C; Parker C M  
CS Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, USA.. william.agace@immuno.lu.se  
NC DK52978 (NIDDK)  
DK42166 (NIDDK)  
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (2000 Mar) 30 (3) 819-26.  
Journal code: EN5. ISSN: 0014-2980.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 200006  
EW 20000604

L4 ANSWER 5 OF 11 MEDLINE  
AN 2000133089 MEDLINE  
DN 20133089  
TI CXCR and CC chemokine receptors on coronary and brain endothelia.  
AU Berger O; Gan X; Gujuluva C; Burns A R; Sulur G; Stins M; Way D; Witte M; Weinand M; Said J; Kim K S; Taub D; Graves M C; Fiala M  
CS Department of Neurology, UCLA School of Medicine, Los Angeles, California 90095-1769, USA.  
NC DA10442 (NIDA)  
NS 26126 (NINDS)  
HL 48493 (NHLBI)  
+  
SO MOLECULAR MEDICINE, (1999 Dec) 5 (12) 795-805.  
Journal code: CG3. ISSN: 1076-1551.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200005  
EW 20000501

L4 ANSWER 6 OF 11 MEDLINE  
AN 2000087135 MEDLINE  
DN 20087135  
TI Increased severity of glomerulonephritis in C-C chemokine receptor 2 knockout mice.  
AU Bird J E; Giancarli M R; Kurihara T; Kowala M C; Valentine M T; Gitlitz P H; Pandya D G; French M H; Durham S K  
CS Division of Metabolic and Cardiovascular Drug Discovery, Bristol Myers Squibb, Princeton, New Jersey 08543, USA.. birdj@bms.com  
SO KIDNEY INTERNATIONAL, (2000 Jan) 57 (1) 129-36.  
Journal code: KVB. ISSN: 0085-2538.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 200005  
EW 20000502

L4 ANSWER 7 OF 11 MEDLINE  
AN 1999410808 MEDLINE  
DN 99410808

TI Expression of CCR2 by endothelial cells : implications for MCP-1 mediated wound injury repair and In vivo inflammatory activation of endothelium.  
AU Weber K S; Nelson P J; Grone H J; Weber C  
CS Institut fur Prophylaxe der Kreislaufkrankheiten, Munchen, Germany..  
kim.weber@klp.med.uni-muenchen.de  
SO ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1999 Sep) 19 (9)  
2085-93.  
Journal code: B89. ISSN: 1079-5642.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199912  
EW 19991202

L4 ANSWER 8 OF 11 MEDLINE  
AN 1999161851 MEDLINE  
DN 99161851  
TI Differential immobilization and hierarchical involvement of chemokines in monocyte arrest and transmigration on inflamed endothelium in shear flow.  
AU Weber K S; von Hundelshausen P; Clark-Lewis I; Weber P C; Weber C  
CS Institut fur Prophylaxe der Kreislaufkrankheiten, Ludwig-Maximilians-Universitat, Munchen, Germany.. kim.weber@klp.med.uni-muenchen.de  
SO EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Feb) 29 (2) 700-12.  
Journal code: EN5. ISSN: 0014-2980.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals; Cancer Journals  
EM 199905  
EW 19990503

L4 ANSWER 9 OF 11 MEDLINE  
AN 1998222152 MEDLINE  
DN 98222152  
TI Mature dendritic cells respond to SDF-1, but not to several beta-chemokines.  
AU Delgado E; Finkel V; Bagiolini M; Mackay C R; Steinman R M;  
Granelli-Piperno A  
CS Laboratory of Cellular Physiology and Immunology, Rockefeller University,  
New York, NY, USA.  
NC AI 40045 (NIAID)  
AI 40874 (NIAID)  
SO IMMUNOBIOLOGY, (1998 Mar) 198 (5) 490-500.  
Journal code: GH3. ISSN: 0171-2985.  
CY GERMANY: Germany, Federal Republic of  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Priority Journals  
EM 199808  
EW 19980801

L4 ANSWER 10 OF 11 MEDLINE  
AN 1998208279 MEDLINE  
DN 98208279  
TI Characterization of the CCR2 chemokine receptor: functional CCR2 receptor expression in B cells.  
AU Frade J M; Mellado M; del Real G; Gutierrez-Ramos J C; Lind P; Martinez-A C  
CS Department of Immunology and Oncology, Centro Nacional de Biotecnologia, Consejo Superior de Investigaciones Cientificas, Campus Cantoblanco, Universidad Autonoma, Madrid, Spain.  
SO JOURNAL OF IMMUNOLOGY, (1997 Dec 1) 159 (11) 5576-84.  
Journal code: IFB. ISSN: 0022-1767.  
CY United States

DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
EM 199806  
EW 19980604

L4 ANSWER 11 OF 11 MEDLINE  
AN 97386611 MEDLINE  
DN 97386611  
TI The amino-terminal domain of the CCR2 chemokine receptor acts as coreceptor for HIV-1 infection.  
AU Frade J M R; Llorente M; Mellado M; Alcami J; Gutierrez-Ramos J C; Zaballos A; Real G; Martinez-A C  
CS Department of Immunology and Oncology, Centro Nacional de Biotecnologia, Consejo Superior de Investigaciones Cientificas, Universidad Autonoma de Madrid, Campus de Cantoblanco, E-28049 Madrid, Spain.  
SO JOURNAL OF CLINICAL INVESTIGATION, (1997 Aug 1) 100 (3) 497-502.  
Journal code: HS7. ISSN: 0021-9738.  
CY United States  
DT Journal; Article; (JOURNAL ARTICLE)  
LA English  
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals  
EM 199711  
EW 19971101

d 15

L5 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS  
AN 2000:84856 CAPLUS  
DN 132:136423  
TI Anti-CCR2 **antibodies** and methods of use therefor  
IN Larosa, Gregory J.; Horvath, Christopher; Newman, Walter  
PA Leukosite, Inc., USA  
SO PCT Int. Appl., 97 pp.  
CODEN: PIXXD2

DT Patent  
LA English

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|      | PATENT NO.      | KIND  | DATE     | APPLICATION NO. | DATE     |
|------|-----------------|---|----------|-----------------|----------|
| PI   | WO 2000005265   | A2  | 20000203 | WO 1999-US16452 | 19990722 |
|      | WO 2000005265   | A3  | 20000427 |                 |          |
|      | W:              | AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ,<br>DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,<br>JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK,<br>MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ,<br>TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ,<br>MD, RU, TJ, TM |          |                 |          |
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|      | AU 9952208      | A1  | 20000214 | AU 1999-52208   | 19990722 |
| PRAI | US 1998-121781  |   | 19980723 |                 |          |
|      | WO 1999-US16452 |   | 19990722 |                 |          |

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L4 11 S L2 AND L3

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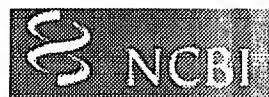


## HIV-1 coreceptor activity of CCR5 and its inhibition by chemokines: independence from G protein signaling and importance of coreceptor downmodulation.

Alkhatib G, Locati M, Kennedy PE, Murphy PM, Berger EA

The Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892, USA.

HIV-1 infection requires the presence of specific chemokine receptors on CD4+ target cells to enable the fusion reactions involved in virus entry. CCR5 is a major fusion coreceptor for macrophage-tropic HIV-1 isolates. HIV-1 entry and fusion are mediated by the viral envelope glycoprotein (Env) and are inhibited by CCR5 ligands, but the mechanisms are unknown. Here, we test the role of G protein signaling and CCR5 surface downmodulation by two separate approaches: direct inactivation of CCR5 signaling by mutagenesis and inactivation of G(i)-type G proteins with pertussis toxin. A CCR5 mutant lacking the last 45 amino acids of the cytoplasmic C-terminus (CCR5306) was created that was expressed on transfected cells at levels comparable to cells expressing CCR5 and displayed normal chemokine binding affinity. CCR5 ligands induced calcium flux and receptor downmodulation in cells expressing CCR5, but not in cells expressing CCR5306. Nevertheless, CCR5 or CCR5306, when coexpressed with CD4, supported comparable HIV-1 Env-mediated cell fusion. Consistent with this, treatment of CCR5-expressing cells with pertussis toxin completely blocked ligand-induced transient calcium flux, but did not affect Env-mediated cell fusion or HIV-1 infection. Also, pertussis toxin did not block chemokine inhibition of Env-mediated cell fusion or HIV-1 infection. However, chemokines inhibited Env-mediated cell fusion less efficiently for CCR5306 than for CCR5. We conclude that the C-terminal domain of CCR5 is critical for G protein signaling and receptor downmodulation from the surface, but that neither function is required for CCR5 fusion coreceptor activity. The contrasting phenotypes of CCR5 and CCR5306 suggest that coreceptor downmodulation and direct blockage of Env interaction sites both contribute to chemokine



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1: *J Leukoc Biol* 1997 Jul;62(1):30-3

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## MCP-1 and CCR2 in HIV infection: regulation of agonist and receptor expression.

Sozzani S, Introna M, Bernasconi S, Polentarutti N, Cinque P, Poli G, Sica A, Mantovani A

Department of Immunology and Cell Biology, Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

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Monocyte chemotactic protein-1 (MCP-1) interacts with the chemokine receptor CCR2. Two CCR2 cDNAs have been described. Sequence analysis as well as Northern blotting and RNase protection with different probes revealed that the CCR2 gene is expressed in activated natural killer (NK) cells and mononuclear phagocytes as a predominant long transcript (3.4 kb) consisting of CCR2B followed by a novel sequence (X), corresponding to an intron in the genome, and by a CCR2A specific portion. The predominant long transcript is polyadenylated and present in the cytoplasm. We found that bacterial products and cytokines affect CCR2 expression. Interleukin-2 (IL-2) augmented CCR2 mRNA in monocytes and NK cells. The augmented migratory capacity of IL-2-activated versus resting NK cells was associated with increased CCR2 transcript levels. Lipopolysaccharide (LPS) and other microbial agents caused a rapid and drastic reduction of CCR2 mRNA levels. The rate of nuclear transcription of CCR2 was not affected by LPS, whereas the mRNA half life was reduced. These results suggest that regulation of receptor expression, in addition to agonist production, is probably a crucial point in the regulation of the chemokine system. Down-regulation of chemokine receptor expression may play a role in the modulation of HIV infection in macrophages by LPS. Levels of MCP-1 were markedly elevated in the cerebrospinal fluid (CSF) but not in blood of HIV-infected patients with cytomegalovirus (CMV) encephalitis. The CSF levels of MCP-1 in CMV encephalitis were markedly higher than those found in the CSF of HIV-infected patients with or without unrelated neurological diseases. IL-8, the prototype of C-X-C chemokines and RANTES and macrophage inflammatory protein-1 alpha (C-C chemokines) were not substantially increased in the liquor of CMV encephalitis patients. High